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## Long-term use of gabapentin and pregabalin as a risk factor for cardiovascular events in patients with type 2 diabetes

*Aims:* This study aimed to investigate whether long-term use of gabapentin and pregabalin in patients with diabetic neuropathy (DPN) is associated with increased risk for adverse cardiovascular events (CVDs).
*Methods:* This retrospective cohort study used propensity score matching within patient electronic health records (EHRs) from 69 healthcare organizations in the US. The study population consisted of 210,064 patients with type 2 diabetes diagnosed with DPN and prescribed DPN medications in their EHRs. Patients were divided into two groups of exposure; patients who received gabapentin or pregabalin; patients who received other medicines for DPN (topiramate, duloxetine, tapentadol, capsaicin, nortriptyline, carbamazepine, venlafaxine, amitriptyline, and mexiletine). The risk of CVDs, including myocardial infarcts (MI), stroke, heart failure (HF), peripheral vascular disease (PVD), and deep venous thromboembolic (DVT) and pulmonary embolism (PE) events, were compared between the two groups. The risk of short- and long-term use was determined within a 3-month and 5-year time frame since the first prescription. Both cohorts were propensity-score matched for covariates, including demographics, risk factors of CVDs, initial drug indications including approved and off-label uses, related medications, adverse socioeconomic circumstances, and specific risk factors for each disease.
*Results:* In patients treated with gabapentin (n≈7000) and pregabalin (n≈4000), the hazard ratio (HR) of 5-year CVDs was respectively (1.14 vs 1.2) for HF, (1.25 vs 1.29) for MI, (1.37 vs 1.35) for PVD, (1.31 vs 1.26) for stroke, (1.58 vs 1.57) for DVT and (1.5 vs 1.28) for PE. The risk of 3-month outcomes in ≈22000 patients treated with gabapentin was increased for DVT (HR: 1.39), PE (HR: 1.27), PVD (HR: 1.17), MI (HR: 1.15) and HF (HR: 1.1) but not stroke. In ≈16500 patients treated with pregabalin for 3 months, there was an increased risk of DVT (HR: 1.27) and PVD (HR: 1.18) but not PE, MI, stroke or HF.
*Conclusions:* This study identified an increased risk of CVDs associated with long-term use of gabapentin and pregabalin in patients with DPN. Short-term gabapentin use was associated with HF, MI, PVD, DVT, and PE. Short-term pregabalin use was only associated with DVT and PE.

**Comments**. This large-scale population study is one of the first to report an increased risk of CVDs, following the long-term use of gabapentin and pregabalin, with the highest risk for DVT. Gabapentin and pregabalin can alter the arterial myogenic tone and cause fluid retention with a possible cascade of increased blood flow turbulence and promotion of endothelial dysfunction, a well-established cardiovascular risk factor. Although these register-based studies are essential, it is vital to acknowledge the data limitations including the generalizability of the results in other countries. In addition, the database identifies only that the medications were prescribed, not consumed. However, the authors only included patients with a second prescription at least 3 years after the first one. There is also no link between whether or not the drugs were prescribed for the treatment of DPN. Furthermore, the medication dosage was not included in this analysis. The cardiovascular risk of these medications could be dose-dependent (as for other adverse events) and low doses may not be associated with an increased risk of CVDs. In conclusion, the long-term use of gabapentin and pregabalin could be another risk factor for CVDs. This calls for thoughtful consideration of risk and benefit when clinicians use these medications.

**Maryam Ferdousi**

**Reference.** Pan Y, Davis PB, Kaebler DC, Blankfield RP, Xu R. Cardiovascular risk of gabapentin and pregabalin in patients with diabetic neuropathy. Cardiovasc Diabetol. 2022 Sep 1;21(1):170. doi: 10.1186/s12933-022-01610-9.
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